

PSJ10 Exh 58

From: Hansen, John <John.Hansen@McKesson.com>
 To: Jinping McCormick
 Sent: 9/2/2011 5:52:34 PM
 Subject: RE: Follow-up discussion re: Actavis oxymorphone campaign
 Attachments: image001.emz

Hi Jinping,

It was good to speak with you earlier today.

Below is a screenshot of McKesson Connect, with an example of an ad for Desonate on the right margin. We will create a similar one for oxymorphone, that links to both the PDF and the ordering page.

Please let me know if you have any questions.

DirectRx Advertising Example

McKESSON
 Empowering Healthcare

John Hansen

Marketing - McKesson Pharmaceutical

Tel: (415) 983-7543

From: Jinping McCormick [mailto:JMCCORMICK@actavis.com]



Sent: Friday, September 02, 2011 3:34 AM
To: Hansen, John
Subject: Re: Follow-up discussion re: Actavis oxymorphone campaign

I'm free during that time. How about I will call you at 10am pacific, 1pm eastern?

Jinping

From: Hansen, John [mailto:John.Hansen@McKesson.com]
Sent: Thursday, September 01, 2011 05:55 PM
To: Jinping McCormick
Cc: Ara Aprahamian RPh; Michael Perfetto; Winter, Wendy <Wendy.Winter@McKesson.com>; Sambrano, Aubrey <Aubrey.Sambrano@McKesson.com>
Subject: RE: Follow-up discussion re: Actavis oxymorphone campaign

Hi Jinping,

Tomorrow I am available between 9:30 and 11:00 Pacific. Let me know if you are free during those times. I don't imagine our conversation will last more than 15 minutes.

Thank you.

John Hansen

Marketing - McKesson Pharmaceutical

Tel: (415) 983-7543

From: Jinping McCormick [mailto:JMCCORMICK@actavis.com]
Sent: Thursday, September 01, 2011 2:44 PM
To: Hansen, John
Cc: Ara Aprahamian RPh; Michael Perfetto; Winter, Wendy; Sambrano, Aubrey
Subject: RE: Follow-up discussion re: Actavis oxymorphone campaign

John,

Sorry I was tied up in another meeting this afternoon and not able to join our discussion.

For the online awareness program, we can use an email HTML file that we have developed to email to all pharmacists. This file is one page with a link to the full prescribing information on our website. I'll forward you the email in a separate email.

For the one-page fax, that will be a challenge as the safety information is mandatory. If the information is developed by McKesson, i.e. no Actavis Logo, but only order information (McKesson ECONO #), would the requirement be different?

I will call you tomorrow to discuss. Let me know a time convenient for you.

Jinping

From: Hansen, John [mailto:John.Hansen@McKesson.com]
Sent: Thursday, September 01, 2011 5:30 PM
To: Jinping McCormick
Cc: Ara Aprahamian RPh; Michael Perfetto; Winter, Wendy; Sambrano, Aubrey
Subject: RE: Follow-up discussion re: Actavis oxymorphone campaign

Hi Jinping,

Thank you for this information.

On our call this afternoon, we discussed using a modified version of the electronic sellsheet as part of an online awareness campaign (via our customer portal) and fax blast.

The majority of the document is devoted to prescribing information, which we understand is mandated by your Legal department. My question is whether you can create a 2-3 page electronic sellsheet that features a link to the more detailed prescribing information?

Also, can we further condense this information down to one page for the fax blast? We cannot fax more than one page to our customers without incurring complaints.

You may be bound by Legal restrictions, but let me know your thoughts on these modifications.

John Hansen

Marketing - McKesson Pharmaceutical

Tel: (415) 983-7543

From: Jinping McCormick [mailto:JMCCORMICK@actavis.com]
Sent: Friday, August 26, 2011 9:38 AM
To: Hansen, John; Winter, Wendy; Sambrano, Aubrey
Cc: Ara Aprahamian RPh; Michael Perfetto
Subject: RE: Follow-up discussion re: Actavis oxymorphone campaign

John and Wendy,

Thank you for the time and effort.

Attached are some background information on the product as well as our ad which is delivered to prescribing physicians and run in August issue of Practical Pain Management and Pharmacy Times. Similar message/graphics is also emailed to all pharmacies around the country about three weeks ago and will be sent again the day after Labor Day.

Here are some suggested talking points to pharmacists:

- We see that you have ordered Opana ER 15mg and 7.5mg in the past and thought you might want to know that
- Generic oxymorphone ER 15mg and 7.5mg are available, fill in the gap since brand discontinued these two strengths
- Generic provided value for you and your patients
- Doctors are starting to write these strengths again, we think it might be helpful for you to have a bottle on the shelf
- We provide incentive to help you get this bottle on the shelf
- If you order by xx date, there is a discount of \$25 for a bottle of 7.5mg and \$50 for 15mg.

Have a good weekend!

<<Oxymorphone Summary for McKesson 8-25-2011.pdf>>

<<Oxymorphone Sellsheet Electronic.pdf>>

Jinping

-----Original Appointment-----

From: Hansen, John [mailto:John.Hansen@McKesson.com]

Sent: Tuesday, August 23, 2011 4:32 PM

To: Winter, Wendy; Sambrano, Aubrey; Jinping McCormick; Ara Aprahamian RPh; Hansen, John

Subject: Follow-up discussion re: Actavis oxymorphone campaign

When: Thursday, August 25, 2011 3:00 PM-3:30 PM (GMT-05:00) Eastern Time (US & Canada).

Where: 1.877.684.9625 Participant code: 737182

When: Thursday, August 25, 2011 12:00 PM-12:30 PM (GMT-08:00) Pacific Time (US & Canada).

Where: 1.877.684.9625 Participant code: 737182

~~*~*~*~*~*~*~*

12:00pm Pacific

Hello,

We'll continue our discussion on the oxymorphone awareness campaign, with additional information on the capabilities of our phone awareness messaging.

**Generic is now
available.**



Oxymorphone Hydrochloride Extended-Release Tablets, CII

Actavis is proud to launch Oxymorphone Hydrochloride Extended-Release Tablets, CII 7.5 mg and 15 mg strengths, immediately available. It is AB rated to Opana[®] ER (oxymorphone hydrochloride) Extended-Release tablets and is indicated for the relief of moderate to severe pain in patients requiring continuous around-the-clock opioid treatment for an extended period of time. At Actavis, we are working to meet the demand for high quality lower-cost alternatives to brand name pharmaceuticals.

Please see the following Boxed Warning and attached for full prescribing information.

IMPORTANT SAFETY INFORMATION

Oxymorphone hydrochloride extended-release tablets contain oxymorphone, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. Oxymorphone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing oxymorphone hydrochloride extended-release tablets in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. Oxymorphone hydrochloride extended-release tablets are an opioid agonist indicated for the relief of moderate to severe pain in patients requiring continuous around-the-clock opioid treatment for an extended period of time. Oxymorphone hydrochloride extended-release tablets are NOT intended for use as an as needed analgesic. Oxymorphone hydrochloride extended-release tablets are to be swallowed whole and are not to be broken, chewed, dissolved, or crushed as this leads to rapid release and absorption of a potentially fatal dose of oxymorphone. Patients must not consume alcoholic beverages, prescription or non prescription medications containing alcohol. Co-ingestion of alcohol with oxymorphone hydrochloride extended-release tablets may result in a potentially fatal overdose of oxymorphone.

Leading the way...with quality generics.

To learn more, call Actavis customer service at 888.925.2342, or visit www.actavis.us.

A321 Rev 6/2011

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actavis
think smart medicine

Now available from Actavis



Oxymorphone Hydrochloride Extended-Release Tablets, CII

- Generic is available in 7.5mg and 15mg strengths
- AB Rated, to Opana ER[®]**
- 100-count bottles
- Another addition to our expanding product portfolio

Product	Strength	Size	NDC#
Oxymorphone Hydrochloride Extended-Release Tablets, CII	7.5 mg	100	0228-3261-11
Oxymorphone Hydrochloride Extended-Release Tablets, CII	15 mg	100	0228-3262-11

To learn more, contact your Actavis representative or wholesaler, or call customer service at 888.925.2342.

Please see attached for full prescribing information

A320 Rev. 7/2011

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use oxymorphone hydrochloride extended-release tablets safely and effectively. See full prescribing information for oxymorphone hydrochloride extended-release tablets.

CII

Oxymorphone Hydrochloride Extended-Release Tablets, 7.5 mg and 15 mg
Initial U.S. Approval: 1959

WARNING: POTENTIAL FOR ABUSE, IMPORTANCE OF PROPER PATIENT SELECTION AND LIMITATIONS OF USE

See full prescribing information for complete boxed warning.

- Oxymorphone hydrochloride extended-release tablets contain oxymorphone which is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to other opioid analgesics. (9)
- Oxymorphone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing oxymorphone hydrochloride extended-release tablets in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. (9)
- Oxymorphone hydrochloride extended-release tablets are NOT intended for use as an as needed analgesic. (1)
- Oxymorphone hydrochloride extended-release tablets are to be swallowed whole and are not to be broken, chewed, dissolved, or crushed as this leads to rapid release and absorption of a potentially fatal dose of oxymorphone. (2)
- Patients must not consume alcoholic beverages, prescription or non-prescription medications containing alcohol. Co-ingestion of alcohol with oxymorphone hydrochloride extended-release tablets may result in a potentially fatal overdose of oxymorphone. (2)

INDICATIONS AND USAGE

- Oxymorphone hydrochloride extended-release tablets are an opioid agonist indicated for the relief of moderate to severe pain in patients requiring continuous around-the-clock opioid treatment for an extended period of time. (1)
- Not intended for use as an as needed analgesic. Not indicated in the immediate post-operative period or if the pain is mild or not expected to persist for an extended period of time. (1)

DOSAGE AND ADMINISTRATION

- Administered on an empty stomach, at least 1 hour prior to or 2 hours after eating. (2.2)
- Symmetrical, every 12h dosing is appropriate for the majority of patients. (2.1)
- Opioid-Naïve Patients: Initiate treatment with 5 mg every 12 hours. (2.2)
- Opioid-Experienced Patients: Ratios as a guide to convert only from other opioids to oxymorphone hydrochloride extended-release tablets. (2.2)
- Individualize treatment; titrate to effective and tolerable dose. (2.1)
- Don't stop abruptly (9.3); taper gradually to stop treatment (2.8)

DOSAGE FORMS AND STRENGTHS

- Extended-Release Tablets, 7.5 mg and 15 mg

CONTRAINDICATIONS

- Known hypersensitivity to oxymorphone, any other ingredients in oxymorphone hydrochloride extended-release tablets, or morphine analogs. (4)
- Respiratory depression (4)
- Acute or severe bronchial asthma or hypercarbia (4)
- Paralytic ileus (4)
- Moderate or severe hepatic impairment (4)

WARNINGS AND PRECAUTIONS**See Boxed WARNINGS**

- Respiratory depression: Increased risk in elderly, debilitated patients, and those suffering from conditions accompanied by hypoxia, hypercapnia, or decreased respiratory reserve. (5.2)
- Misuse, abuse, and diversion: Oxymorphone hydrochloride extended-release tablets are an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine. (5.3)
- CNS effects: Additive CNS-depressive effects when used in conjunction with alcohol, other opioids, or illicit drugs. (5.4)
- Head Injury: Effects may be markedly exaggerated. Administer with extreme caution. (5.5)
- Hypotensive effect: Increased risk with compromised ability to maintain blood pressure. Administer with caution to patients in circulatory shock. (5.6)
- Mild hepatic impairment: Use with caution and at lower doses due to higher plasma concentrations than in patients with normal hepatic function. (5.7)
- Prolonged gastric obstruction: May occur in patients with gastrointestinal obstruction. (5.9)
- Sphincter of Oddi: Administer with caution in patients with biliary tract disease. (5.11)
- Impaired mental/physical abilities: Caution must be used with potentially hazardous activities (5.12)

ADVERSE REACTIONS

Adverse reactions in ≥2% of patients in placebo-controlled trials: nausea, constipation, dizziness, somnolence, vomiting, pruritus, headache, sweating increased, dry mouth, sedation, diarrhea, insomnia, fatigue, appetite decreased, and abdominal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Actavis at (1-800-432-8534) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- CNS depressants: Increased risk of respiratory depression, hypotension, profound sedation, coma or death. When combined therapy with CNS depressant is contemplated, the dose of one or both agents should be reduced. (7.2)
- Mixed agonist/antagonist opioids (i.e., pentazocine, nalbuphine, and butorphanol): May reduce analgesic effect and/or precipitate withdrawal symptoms. (7.3)
- Cimetidine: Combination use may precipitate confusion, disorientation, respiratory depression, apnea, seizures. (7.4)
- Anticholinergics: May result in urinary retention and/or severe constipation, which may lead to paralytic ileus. (7.5)
- Monoamine oxidase inhibitors (MAOIs): Potentiate the action of opioids. Oxymorphone hydrochloride extended-release tablets should not be used in patients taking MAOIs or within 14 days of stopping such treatment. (7.6)
- Dose adjustment for CYP3A4/50 or 2C9-mediated drug-drug interactions is not required. (7.1)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Not recommended during labor and delivery, pregnancy, or nursing. (8.1)
- Geriatric Patients — Oxymorphone hydrochloride extended-release should be used with caution in elderly patients. (8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA – approved patient labeling

Revised: 10/2010

FULL PRESCRIBING INFORMATION: CONTENTS***BOXED WARNING****1 INDICATIONS AND USAGE****2 DOSAGE AND ADMINISTRATION**

2.1 Safe Administration Instructions

2.2 Initiation of Therapy with Oxycodone Hydrochloride
Extended-Release Tablets

2.3 Patients with Hepatic Impairment

2.4 Patients with Renal Impairment

2.5 Use with Central Nervous System Depressants

2.6 Geriatric Patients

2.7 Maintenance of Therapy

2.8 Cessation of Therapy

3 DOSAGE FORMS AND STRENGTHS**4 CONTRAINDICATIONS****5 WARNINGS AND PRECAUTIONS**

5.1 Information Essential for Safe Administration

5.2 Respiratory Depression

5.3 Misuse, Abuse and Diversion of Opioids

5.4 Interactions with Alcohol and other CNS Depressants

5.5 Use in Patients with Head Injury and Increased Intracranial Pressure

5.6 Hypotensive Effect

5.7 Hepatic Impairment

5.8 Special Risk Groups

5.9 Gastrointestinal Effects

5.10 Ambulatory Surgery and Post Operative Use

5.11 Use in Pancreatic/Biliary Tract Disease

5.12 Driving and Operating Machinery

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

7 DRUG INTERACTIONS

7.1 Drug-Drug Interactions

7.2 Use in CNS Depressants

7.3 Interactions with Mixed Agonist/Antagonist Opioid Analgesics

7.4 Cimetidine

7.5 Anticholinergics

7.6 MAO Inhibitors

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Hepatic Impairment

8.7 Renal Impairment

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

10.1 Symptoms

10.2 Treatment

11 DESCRIPTION**12 CLINICAL PHARMACOLOGY**

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, mutagenesis, impairment of fertility

14 CLINICAL STUDIES

14.1 12-Week Study in Opioid-Naïve Patients with Low Back Pain

14.2 12-Week Study in Opioid-Experienced Patients with Low Back Pain

16 HOW SUPPLIED/STORAGE AND HANDLING**17 PATIENT COUNSELING INFORMATION**

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION**WARNING: POTENTIAL FOR ABUSE, IMPORTANCE OF PROPER PATIENT SELECTION AND LIMITATIONS OF USE****Potential for Abuse**

Oxymorphone hydrochloride extended-release tablets contain oxymorphone, which is a morphine-like opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. (9)

Oxymorphone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing oxymorphone hydrochloride extended-release tablets in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. (9.2)

Proper Patient Selection

Oxymorphone hydrochloride extended-release tablets are an extended-release oral formulation of oxymorphone indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. (1)

Limitations of Use

Oxymorphone hydrochloride extended-release tablets are NOT intended for use as an as needed analgesic. (1)

Oxymorphone hydrochloride extended-release tablets are to be swallowed whole and are not to be broken, chewed, dissolved, or crushed. Taking broken, chewed, dissolved, or crushed oxymorphone hydrochloride extended-release tablets leads to rapid release and absorption of a potentially fatal dose of oxymorphone. (2)

Patients must not consume alcoholic beverages, or prescription or non-prescription medications containing alcohol, while on oxymorphone hydrochloride extended-release tablet therapy. The co-ingestion of alcohol with oxymorphone hydrochloride extended-release tablets may result in increased plasma levels and a potentially fatal overdose of oxymorphone. (2)

1 INDICATIONS AND USAGE

Oxymorphone hydrochloride extended-release tablets are indicated for the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time.

Limitations of Usage

Oxymorphone hydrochloride extended-release tablets are not intended for use as an as needed analgesic.

Oxymorphone hydrochloride extended-release tablets are not indicated for pain in the immediate post-operative period if the pain is mild, or not expected to persist for an extended period of time.

Oxymorphone hydrochloride extended-release tablets are only indicated for post-operative use if the patient is already receiving the drug prior to surgery or if the post-operative pain is expected to be moderate or severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. (See American Pain Society guidelines).

2 DOSAGE AND ADMINISTRATION**2.1 Safe Administration Instructions**

Oxymorphone hydrochloride extended-release tablets are to be swallowed whole and are not to be broken, chewed, dissolved, or crushed. Taking broken, chewed, dissolved, or crushed oxymorphone hydrochloride extended-release tablets leads to rapid release and absorption of a potentially fatal dose of oxymorphone.

Patients must not consume alcoholic beverages, or prescription or non-prescription medications containing alcohol, while on oxymorphone hydrochloride extended-release tablet therapy. The co-ingestion of alcohol with oxymorphone hydrochloride extended-release tablets may result in increased plasma levels and a potentially fatal overdose of oxymorphone.

While symmetric (same dose AM and PM), around-the-clock, every 12 hours dosing is appropriate for the majority of patients, some patients may benefit from asymmetric (different dose given in AM than in PM) dosing, tailored to their pain pattern. It is usually appropriate to treat a patient with only one extended-release opioid for around-the-clock therapy.

Selection of patients for treatment with oxymorphone hydrochloride extended-release tablets should be governed by the same principles that apply to the use of other extended-release opioid analgesics [see *Indications and Usage (1)*]. Physicians should individualize treatment in every case, using non-opioid analgesics, opioids on an as needed basis, combination products, and chronic opioid therapy in a progressive plan of pain management such as outlined by the World Health Organization, the American Pain Society and the Federation of State Medical Boards Model Guidelines. Healthcare professionals should follow appropriate pain management principles of careful assessment and ongoing monitoring [see *Boxed Warning*].

2.2 Initiating Therapy with Oxymorphone Hydrochloride Extended-Release Tablets

It is necessary to adjust the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience. In the selection of the initial dose of oxymorphone hydrochloride extended-release tablets, attention should be given to the following:

- total daily dose, potency and specific characteristics of the opioid the patient has been taking previously;
- relative potency estimate used to calculate the equivalent oxymorphone dose needed;
- patient's degree of opioid tolerance;
- age, general condition, and medical status of the patient;
- concurrent non-opioid analgesics and other medications;
- type and severity of the patient's pain;
- balance between pain control and adverse experiences;
- risk factors for abuse or addiction, including a prior history of abuse or addiction.

Once therapy is initiated, frequently assess pain relief and other opioid effects. Base the titration of the total daily oxymorphone hydrochloride extended-release tablet dose upon the amount of supplemental opioid utilization, severity of the patient's pain, and the patient's ability to tolerate the opioid. Titrate dose to generally mild or no pain with the regular use of no more than two doses of supplemental analgesia, i.e. "rescue," per 24 hours. Patients who experience breakthrough pain may require dosage adjustment.

If signs of excessive opioid-related adverse experiences are observed, the next dose may be reduced. If this adjustment leads to inadequate analgesia, a supplemental dose of an immediate-release opioid, or a non-opioid analgesic may be administered. Adjust dosing to obtain an appropriate balance between pain relief and opioid-related adverse experiences. If significant adverse events occur before the therapeutic goal of mild or no pain is achieved, the events should be treated aggressively. Once adverse events are adequately managed, continue upward titration to an acceptable level of pain control.

During periods of changing analgesic requirements, including initial titration, frequent contact is recommended between physician, other members of the healthcare team, the patient and the caregiver/family. Advise patients and caregivers/family members of the potential adverse reactions.

The dosing recommendations below, therefore, can only be considered as suggested approaches to what is actually a series of clinical decisions over time in the management of the pain of each individual patient.

Titrate dose to adequate pain relief (generally mild or no pain).

Administer oxymorphone hydrochloride extended-release tablets on an empty stomach, at least one hour prior to or two hours after eating [see *Clinical Pharmacology (12.3)*].

Opioid-Naïve Patients

The initial dose for patients who are not opioid-experienced and who are being initiated on chronic around-the-clock opioid therapy with oxymorphone hydrochloride extended-release tablets is 5 mg every 12 hours. Thereafter, titrate the dose individually at increments of 5 to 10 mg every 12 hours every 3 to 7 days, to a level that provides adequate analgesia and minimizes side effects under the close supervision of the prescribing physician.

Opioid-Experienced Patients

Conversion from Oxymorphone Hydrochloride Tablets to Oxymorphone Hydrochloride Extended-Release Tablets

Patients receiving oxymorphone hydrochloride tablets may be converted to oxymorphone hydrochloride extended-release tablets by administering half the patient's total daily oral oxymorphone hydrochloride tablets dose as oxymorphone hydrochloride extended-release tablets, every 12 hours.

Conversion from Parenteral Oxymorphone to Oxymorphone Hydrochloride Extended-Release Tablets

Given oxymorphone hydrochloride extended-release tablet's absolute oral bioavailability of approximately 10%, patients receiving parenteral oxymorphone may be converted to oxymorphone hydrochloride extended-release tablets by administering 10 times the patient's total daily parenteral oxymorphone dose as oxymorphone hydrochloride extended-release tablets in two equally divided doses (e.g., [IV dose x 10] divided by 2). Due to patient variability with regards to opioid analgesic response, upon conversion monitor patients closely to evaluate for adequate analgesia and side effects.

Conversion from Other Oral Opioids to Oxymorphone Hydrochloride Extended-Release Tablets

For conversion from other opioids to oxymorphone hydrochloride extended-release tablets, physicians and other healthcare professionals are advised to refer to published relative potency information, keeping in mind that conversion ratios are only approximate. In general, it is safest to start the oxymorphone hydrochloride extended-release tablets therapy by administering half of the calculated total daily dose of oxymorphone hydrochloride extended-release tablets (see conversion ratio table below) in 2 divided doses, every 12 hours. Gradually adjust the initial dose of oxymorphone hydrochloride extended-release tablets until adequate pain relief and acceptable side effects have been achieved.

The following table provides approximate equivalent doses, which may be used as a guideline for conversion. **The conversion ratios and approximate equivalent doses in this conversion table are only to be used for the conversion from current opioid therapy to oxymorphone hydrochloride extended-release tablets.** In a Phase 3 clinical trial with an open-label titration period, patients were converted from their current opioid to oxymorphone hydrochloride extended-release tablets using the following table as a guide. There is substantial patient variation in the relative potency of different opioid drugs and formulations.

CONVERSION RATIOS TO OXYMORPHONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS

Opioid	Approximate Equivalent Dose	Oral
	Oral	Conversion Ratio ^a
Oxymorphone	10 mg	1
Hydrocodone	20 mg	0.5
Oxycodone	20 mg	0.5
Methadone ^b	20 mg	0.5
Morphine	30 mg	0.333

^aRatio for conversion of oral opioid dose to approximate oxymorphone equivalent dose. Select opioid and multiply the dose by the conversion ratio to calculate the approximate oral oxymorphone equivalent.

- **The conversion ratios and approximate equivalent doses in this conversion table are only to be used for the conversion from current opioid therapy to oxymorphone hydrochloride extended-release tablets.**
- Sum the total daily dose for the opioid and multiply by the conversion ratio to calculate the oxymorphone total daily dose.
- For patients on a regimen of mixed opioids, calculate the approximate oral oxymorphone dose for each opioid and sum the totals to estimate the total daily oxymorphone dose.
- The dose of oxymorphone hydrochloride extended-release tablets can be gradually adjusted, preferably at increments of 10 mg every 12 hours every 3 to 7 days, until adequate pain relief and acceptable side effects have been achieved [see *Dosage and Administration* (2.1)].

^b **It is extremely important to monitor all patients closely when converting from methadone to other opioid agonists.** The ratio between methadone and other opioid agonists may vary widely as a function of previous dose exposure. Methadone has a long half-life and tends to accumulate in the plasma.

No dose adjustment for CYP 3A4-or 2C9-mediated drug-drug interactions is required [see *Clinical Pharmacology* (12.3)].

2.3 Patients with Hepatic Impairment

Start patients with mild hepatic impairment with the lowest dose and titrate slowly while carefully monitoring side effects. Oxymorphone hydrochloride extended-release tablets are contraindicated in patients with moderate or severe hepatic impairment [see *Warnings and Precautions* (5.7) and *Clinical Pharmacology* (12.3)].

2.4 Patients with Renal Impairment

There are 57% and 65% increases in oxymorphone bioavailability in patients with moderate and severe renal impairment, respectively [see *Clinical Pharmacology* (12.3)]. Accordingly, in patients with creatinine clearance rates less than 50 mL/min, start oxymorphone hydrochloride extended-release tablets with the lowest dose and titrate slowly while carefully monitoring side effects.

2.5 Use with Central Nervous System Depressants

In patients who are concurrently receiving other central nervous system (CNS) depressants including sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers, and alcohol, start oxymorphone hydrochloride extended-release tablets at 1/3 to 1/2 of the usual dose because respiratory depression, hypotension, and profound sedation, coma or death may result [see *Warnings and Precautions* (5.4) and *Drug Interactions* (7.2)].

Although no specific interaction between oxymorphone and monoamine oxidase inhibitors has been observed, oxymorphone hydrochloride extended-release tablets are not recommended for use in patients who have received MAO inhibitors within 14 days [see *Drug Interactions* (7.6)].

2.6 Geriatrics Patients

The steady-state plasma concentrations of oxymorphone are approximately 40% higher in elderly subjects than in young subjects. Exercise caution in the selection of the starting dose of oxymorphone hydrochloride extended-release tablets for an elderly patient by starting at the low end of the dosing range and slowly titrating to adequate analgesia [see *Clinical Pharmacology* (12.3) and *Use in Specific Populations* (8.5)].


2.7 Maintenance of Therapy


During chronic therapy with oxymorphone hydrochloride extended-release tablets, periodically reassess the continued need for around-the-clock opioid therapy. Continue to assess patients for their clinical risks for opioid abuse, addiction, or diversion particularly with high-dose formulations. If patients need to titrate while on maintenance therapy, follow the same method outlined in *Initiating Therapy with Oxymorphone Hydrochloride Extended-Release Tablets*.

2.8 Cessation of Therapy

When the patient no longer requires therapy with oxymorphone hydrochloride extended-release tablets, gradually taper doses to prevent signs and symptoms of withdrawal in the physically dependent patient.

3 DOSAGE FORMS AND STRENGTHS

The 7.5 mg dosage form are gray, round tablets, debossed with “” on one side and “261” on the other side.

The 15 mg dosage form are white to off-white, round tablets, debossed with “” on one side and “262” on the other side.

4 CONTRAINDICATIONS

Oxymorphone hydrochloride extended-release tablets are contraindicated in patients who have:

- significant respiratory depression
- or are suspected of having paralytic ileus
- acute or severe bronchial asthma or hypercarbia
- moderate and severe hepatic impairment [see *Clinical Pharmacology* (12.3), *Warnings and Precautions* (5.7)].
- known hypersensitivity to any of its components or the active ingredient, oxymorphone or with known hypersensitivity to morphine analogs such as codeine.

5 WARNINGS AND PRECAUTIONS

5.1 Information Essential for Safe Administration

Oxymorphone hydrochloride extended-release tablets are to be swallowed whole, and are not to be broken, chewed, crushed or dissolved. Taking broken, chewed, crushed or dissolved oxymorphone hydrochloride extended-release tablets could lead to the rapid release and absorption of a potentially fatal dose of oxymorphone [see *Boxed Warning*].

Patients must not consume alcoholic beverages, or prescription or non-prescription medications containing alcohol, while on oxymorphone hydrochloride extended-release tablets therapy. The co-ingestion of alcohol with oxymorphone hydrochloride extended-release tablets may result in increased plasma levels and a potentially fatal overdose of oxymorphone [see *Pharmacokinetics* (12.3)].

Instruct patients against use by individuals other than the patient for whom oxymorphone hydrochloride extended-release tablets were prescribed, as such inappropriate use may have severe medical consequences, including death.

5.2 Respiratory Depression

Respiratory depression is the chief hazard of oxymorphone hydrochloride extended-release tablets. Respiratory depression is a potential problem in elderly or debilitated patients as well as in those suffering from conditions accompanied by hypoxia or hypercapnia when even moderate therapeutic doses may dangerously decrease pulmonary ventilation.

Administer oxymorphone hydrochloride extended-release tablets with extreme caution to patients with conditions accompanied by hypoxia, hypercapnia, or decreased respiratory reserve such as: asthma, chronic obstructive pulmonary disease or cor pulmonale, severe obesity, sleep apnea syndrome, myxedema, kyphoscoliosis, CNS depression or coma. In these patients, even usual therapeutic doses of oxymorphone may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea. Consider alternative non-opioid analgesics and use oxymorphone hydrochloride extended-release tablets only under careful medical supervision at the lowest effective dose in such patients.

5.3 Misuse, Abuse and Diversion of Opioids

Oxymorphone hydrochloride extended-release tablets contain oxymorphone, a mu opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine. Opioid agonists are sought by drug abusers and people with addiction disorders and are subject to criminal diversion.

Oxymorphone can be abused in a manner similar to other opioid agonists, legal or illicit. This issue should be considered when prescribing or dispensing oxymorphone in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

Oxymorphone hydrochloride extended-release tablets may be abused by crushing, chewing, snorting or injecting the product. These practices will result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death [see *Drug Abuse and Dependence* (9)].

Oxymorphone hydrochloride extended-release tablets may be targeted for theft and diversion. Healthcare professionals should contact their State Medical Board, State Board of Pharmacy, or State Control Board for information on how to detect or prevent diversion of this product, and security requirements for storing and handling of oxymorphone hydrochloride extended-release tablets.

Healthcare professionals should advise patients to store oxymorphone hydrochloride extended-release tablets in a secure place, preferably locked and out of the reach of children and other non-caregivers.

Concerns about abuse, misuse, diversion and addiction should not prevent the proper management of pain.

5.4 Interactions with Alcohol and other CNS Depressants

Patients receiving other opioid analgesics, general anesthetics, phenothiazines or other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol) concomitantly with oxymorphone may experience respiratory depression, hypotension, profound sedation, coma and death [see *Drug Interactions* (7.2)]. Avoid concurrent use of alcohol and oxymorphone hydrochloride extended-release tablets [see *Pharmacokinetics* (12.3)].

5.5 Use in Patients with Head Injury and Increased Intracranial Pressure

In the presence of head injury, intracranial lesions or a preexisting increase in intracranial pressure, the possible respiratory depressant effects of opioid analgesics and their potential to elevate cerebrospinal fluid pressure (resulting from vasodilation following CO₂ retention) may be markedly exaggerated. Furthermore, opioid analgesics can produce effects on papillary response and consciousness, which may obscure neurologic signs of further increases in intracranial pressure in patients with head injuries.

Administer oxymorphone hydrochloride extended-release tablets with extreme caution to patients who may be particularly susceptible to the intracranial effects of CO₂ retention, such as those with evidence of increased intracranial pressure or impaired consciousness. Opioids may obscure the clinical course of a patient with a head injury and should be used only if clinically warranted.

5.6 Hypotensive Effect

Oxymorphone hydrochloride extended-release tablets may cause severe hypotension in a patient whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents that compromise vasomotor tone. Administer oxymorphone hydrochloride extended-release tablets with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

5.7 Hepatic Impairment

A study of oxymorphone hydrochloride extended-release tablets in patients with hepatic disease indicated greater plasma concentrations than those with normal hepatic function [See *Clinical Pharmacology* (12)]. Use oxymorphone hydrochloride extended-release tablets with caution in patients with mild impairment, starting with the lowest dose and titrating slowly while carefully monitoring for side effects [see *Dosage and Administration* (2.3)]. Oxymorphone hydrochloride extended-release tablets are contraindicated in patients with moderate or severe hepatic impairment.

5.8 Special Risk Groups

Use oxymorphone hydrochloride extended-release tablets with caution in the following conditions: adrenocortical insufficiency (e.g., Addison's disease), prostatic hypertrophy or urethral stricture, severe impairment of pulmonary or renal function, and toxic psychosis.

Opioids may aggravate convulsions in patients with convulsive disorders, and may induce or aggravate seizures in some clinical settings.

5.9 Gastrointestinal Effects

Oxymorphone hydrochloride extended-release decreases bowel motility. Opioids diminish propulsive peristaltic waves in the gastrointestinal tract. Monitor for decreased bowel motility in post-operative patients receiving opioids. The administration of oxymorphone hydrochloride extended-release may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Oxymorphone hydrochloride extended-release tablets are contraindicated in patients with paralytic ileus.

5.10 Ambulatory Surgery and Post-Operative Use

Oxymorphone hydrochloride extended-release tablets are not indicated for pre-emptive analgesia (administration pre-operatively for the management of post-operative pain).

Oxymorphone hydrochloride extended-release tablets are only indicated for postoperative use in the patient if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate (see American Pain Society guidelines).

Patients who are already receiving oxymorphone hydrochloride extended-release tablets as part of ongoing analgesic therapy may be safely continued on the drug if appropriate dosage adjustments are made considering the procedure, other drugs given, and the temporary changes in physiology caused by the surgical intervention.

5.11 Use in Pancreatic/Biliary Tract Disease

Oxymorphone hydrochloride extended-release tablets, like other opioids, may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis.

5.12 Driving and Operating Machinery

Opioid analgesics impair the mental and physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Respiratory depression [see *Warnings and Precautions* (5.2)]
- Misuse and abuse [see *Warning and Precautions* (5.3) and *Drug Abuse and Dependence* (9)]
- CNS depressant effects [see *Warnings and Precautions* (5.4)]

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety of oxymorphone hydrochloride extended-release tablets was evaluated in a total of 2011 patients in controlled clinical trials. The clinical trials consisted of patients with moderate to severe chronic non-malignant pain, cancer pain, and post surgical pain.

Tables 1 and 2 list the most frequently occurring adverse reactions (in at least 5% of patients) from the placebo-controlled trials in patients with low back pain.

Table 1: Treatment-Emergent Adverse Events Reported in $\geq 5\%$ of Patients During the Open-Label Titration Period and Double-Blind Treatment Period by Preferred Term —Number (%) of Treated Patients (12-Week Study in Opioid-Naïve Patients with Low Back Pain)

	Open-Label Titration Period	Double-Blind Treatment Period	
	Oxymorphone Hydrochloride Extended-Release Tablets	Oxymorphone Hydrochloride Extended-Release Tablets	Placebo
Preferred Term	(N = 325)	(N = 105)	(N = 100)
Constipation	26%	7%	1%
Somnolence	19%	2%	0%
Nausea	18%	11%	9%
Dizziness	11%	5%	3%
Headache	11%	4%	2%
Pruritus	7%	3%	1%

Table 2. Treatment-Emergent Adverse Events Reported in $\geq 5\%$ of Patients During the Open-Label Titration Period and Double-Blind Treatment Period by Preferred Term —Number (%) of Treated Patients (12-Week Study In Opioid-Experienced Patients with Low Back Pain)

	Open-Label Titration Period	Double-Blind Treatment Period	
	Oxymorphone Hydrochloride Extended-Release Tablets	Oxymorphone Hydrochloride Extended-Release Tablets	Placebo
Preferred Term	(N = 250)	(N = 70)	(N = 72)
Nausea	20%	3%	1%
Constipation	12%	6%	1%
Headache	12%	3%	0%
Somnolence	11%	3%	0%
Vomiting	9%	0%	1%
Pruritus	8%	0%	0%
Dizziness	6%	0%	0%

The following table lists adverse reactions that were reported in at least 2% of patients in placebo-controlled trials (N=5).

Table 3: Adverse Reactions Reported in Placebo-Controlled Clinical Trials with Incidence $\geq 2\%$ in Patients Receiving Oxymorphone Hydrochloride Extended-Release Tablets.

MedDRA Preferred Term	Oxymorphone Hydrochloride Extended-Release Tablets (N=1259)	Placebo (N=461)
Nausea	33%	13%
Constipation	28%	13%
Dizziness (Excl Vertigo)	18%	8%
Somnolence	17%	2%
Vomiting	16%	4%
Pruritus	15%	8%
Headache	12%	6%
Sweating increased	9%	9%
Dry mouth	6%	<1%
Sedation	6%	8%
Diarrhea	4%	6%
Insomnia	4%	2%
Fatigue	4%	1%
Appetite decreased	3%	<1%
Abdominal pain	3%	2%

The common ($\geq 1\%$ to $<10\%$) adverse drug reactions reported at least once by patients treated with oxymorphone hydrochloride extended-release tablets in the clinical trials organized by MedDRA's (Medical Dictionary for Regulatory Activities) System Organ Class and not represented in Table 1 were:

Eye disorders: vision blurred

Gastrointestinal disorders: diarrhea, abdominal pain, dyspepsia

General disorders and administration site conditions: dry mouth, appetite decreased, fatigue, lethargy, weakness, pyrexia, dehydration, weight decreased, edema

Nervous system disorders: insomnia

Psychiatric disorders: anxiety, confusion, disorientation, restlessness, nervousness, depression

Respiratory, thoracic and mediastinal disorders: dyspnea

Vascular disorders: flushing and hypertension

Other **less common** adverse reactions known with opioid treatment that were seen <1% in the oxymorphone hydrochloride extended-release tablets trials include the following: Bradycardia, palpitation, syncope, tachycardia, postural hypotension, miosis, visual disturbance, abdominal distention, ileus, feeling jittery, hot flashes, allergic reactions, hypersensitivity, urticaria, oxygen saturation decreased, central nervous system depression, depressed level of consciousness, agitation, dysphoria, euphoric mood, hallucination, mental impairment, mental status changes, difficult micturition, urinary retention, hypoxia, respiratory depression, respiratory distress, respiratory rate decreased, clamminess, dermatitis, hypotension.

7 DRUG INTERACTIONS

7.1 Drug-Drug Interactions

Oxymorphone is highly metabolized principally in the liver and undergoes reduction or conjugation with glucuronic acid to form both active and inactive metabolites [see *Pharmacokinetics (12.3)*]. Clinical drug interaction studies with oxymorphone hydrochloride extended-release tablets showed no induction of CYP450 3A4 or 2C9 enzyme activity, indicating that no dose adjustment for CYP 3A4- or 2C9-mediated drug-drug interactions is required [see *Clinical Pharmacology (12.3)*].

7.2 Use with CNS Depressants

The concomitant use of other CNS depressants including sedatives, hypnotics, tranquilizers, general anesthetics, phenothiazines, other opioids, and alcohol may produce additive CNS depressant effects. Oxymorphone hydrochloride extended-release tablets should be started at 1/3 to 1/2 of the usual dose in patients who are concurrently receiving other central nervous system depressants because respiratory depression, hypotension, and profound sedation, coma and death may result, and titrated slowly as necessary for adequate pain relief.

When combined therapy with any of the above medications is considered, the dose of one or both agents should be reduced [see *Dosage and Administration (2.5)* and *Warnings and Precautions (5.4)*].

7.3 Interactions with Mixed Agonist/Antagonist Opioid Analgesics

Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, butorphanol, or buprenorphine) should be administered with caution to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic, such as oxymorphone. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of oxymorphone and/or may precipitate withdrawal symptoms.

7.4 Cimetidine

CNS side effects have been reported (e.g., confusion, disorientation, respiratory depression, apnea, seizures) following coadministration of cimetidine with opioid analgesics; a causal relationship has not been established.

7.5 Anticholinergics

Anticholinergics or other medications with anticholinergic activity when used concurrently with opioid analgesics may result in increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.

7.6 MAO Inhibitors

Oxymorphone hydrochloride extended-release tablets are not recommended for use in patients who have received MAO inhibitors within 14 days, because severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics. No specific interaction between oxymorphone and MAO inhibitors has been observed, but caution in the use of any opioid in patients taking this class of drugs is appropriate.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

The safety of using oxymorphone in pregnancy has not been established with regard to possible adverse effects on fetal development. The use of oxymorphone hydrochloride extended-release tablets in pregnancy, in nursing mothers, or in women of child-bearing potential requires that the possible benefits of the drug be weighed against the possible hazards to the mother and the child.

Prolonged use of opioid analgesics during pregnancy may cause fetal-neonatal physical dependence.

Teratogenic EffectsPregnancy Category C

There are no adequate and well-controlled studies of oxymorphone in pregnant women. Oxymorphone hydrochloride extended-release tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus [see *Use in Specific Populations* (8.2)].

Oxymorphone hydrochloride administration did not cause malformations at any doses evaluated during developmental toxicity studies in rats (≤ 25 mg/kg/day) or rabbits (≤ 50 mg/kg/day). These doses are ~3-fold and ~12-fold the human dose of 40 mg every 12 hours, based on body surface area. There were no developmental effects in rats treated with 5 mg/kg/day or rabbits treated with 25 mg/kg/day. Fetal weights were reduced in rats and rabbits given doses of ≥ 10 mg/kg/day and 50 mg/kg/day, respectively. These doses are ~1.2-fold and ~12-fold the human dose of 40 mg every 12 hours based on body surface area, respectively. There were no effects of oxymorphone hydrochloride on intrauterine survival in rats at doses ≤ 25 mg/kg/day, or rabbits at ≤ 50 mg/kg/day in these studies (see Non-teratogenic Effects, below). In a study that was conducted prior to the establishment of Good Laboratory Practices (GLP) and not according to current recommended methodology, a single subcutaneous injection of oxymorphone hydrochloride on gestation day 8 was reported to produce malformations in offspring of hamsters that received 15.5-fold the human dose of 40 mg every 12 hours based on body surface area. This dose also produced 20% maternal lethality.

Non-teratogenic Effects

Oxymorphone hydrochloride administration to female rats during gestation in a pre- and postnatal developmental toxicity study reduced mean litter size (18%) at a dose of 25 mg/kg/day, attributed to an increased incidence of stillborn pups. An increase in neonatal death occurred at ≥ 5 mg/kg/day. Post-natal survival of the pups was reduced throughout weaning following treatment of the dams with 25 mg/kg/day. Low pup birth weight and decreased postnatal weight gain occurred in pups born to oxymorphone-treated pregnant rats given a dose of 25 mg/kg/day. This dose is ~3-fold higher than the human dose of 40 mg every 12 hours on a body surface area basis.

8.2 Labor and Delivery

Opioids cross the placenta and may produce respiratory depression in neonates. Oxymorphone hydrochloride extended-release tablets are not recommended for use in women during and immediately prior to labor, when use of shorter acting analgesics or other analgesic techniques are more appropriate. Occasionally, opioid analgesics may prolong labor through actions which temporarily reduce the strength, duration and frequency of uterine contractions. However this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor.

Neonates whose mothers received opioid analgesics during labor should be observed closely for signs of respiratory depression. A specific opioid antagonist, such as naloxone or nalmeferene, should be available for reversal of opioid-induced respiratory depression in the neonate.

Upon delivery from a mother who received opioids for a long period of time, neonatal withdrawal may occur. Symptoms usually appear during the first days of life and may include convulsions, irritability, excessive crying, tremors, hyperactive reflexes, fever, vomiting, diarrhea, sneezing, yawning, and increased respiratory rate.

8.3 Nursing Mothers

It is not known whether oxymorphone is excreted in human milk. Because many drugs, including some opioids, are excreted in human milk, caution should be exercised when oxymorphone hydrochloride extended-release tablets are administered to a nursing woman. Infants exposed to oxymorphone hydrochloride extended-release through breast milk should be monitored for excess sedation and respiratory depression. Withdrawal symptoms can occur in breast-fed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

8.4 Pediatric Use

Safety and effectiveness of oxymorphone hydrochloride extended-release tablets in pediatric patients below the age of 18 years have not been established.

8.5 Geriatric Use

Oxymorphone hydrochloride extended-release tablets should be used with caution in elderly patients [see *Clinical Pharmacology* (12.3)].

Of the total number of subjects in clinical studies of oxymorphone hydrochloride extended-release tablets, 27% were 65 and over, while 9% were 75 and over. No overall differences in effectiveness were observed between these subjects and younger subjects. There were several adverse events that were more frequently observed in subjects 65 and over compared to younger subjects. These adverse events included dizziness, somnolence, confusion, and nausea.

8.6 Hepatic Impairment

In a PK study of oxymorphone hydrochloride extended-release, patients with mild hepatic impairment were shown to have an increase in bioavailability of 1.6 fold. Use oxymorphone hydrochloride extended-release tablets with caution in patients with mild impairment. Start these patients on the lowest dose and titrate slowly while carefully monitoring for side effects. Oxymorphone hydrochloride extended-release tablets are contraindicated for patients with moderate and severe hepatic impairment [see *Contraindications* (4), *Warnings and Precautions* (5.7), and *Dosage and Administration* (2.3)].

8.7 Renal Impairment

In a PK study of oxymorphone hydrochloride extended-release, patients with moderate to severe renal impairment were shown to have an increase in bioavailability ranging from 57 to 65% [see *Clinical Pharmacology* (12.3)]. Start these patients with the lowest dose of oxymorphone hydrochloride extended-release tablets and titrate slowly while monitored for side effects [see *Dosage and Administration* (2.4)].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Oxymorphone hydrochloride extended-release tablets contain oxymorphone, a mu opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine and other opioids. Oxymorphone can be abused and is subject to criminal diversion [see *Warning and Precautions* (5.3)].

9.2 Abuse

All patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use. Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. Addiction is characterized by one or more of the following: impaired control over drug use, compulsive use, use for non-medical purposes, and continued use despite harm. Drug addiction is a treatable disease, utilizing a multidisciplinary approach, but relapse is common.

"Drug seeking" behavior is very common to addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated claims of loss of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" (visiting multiple prescribers) to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. Oxymorphone hydrochloride extended-release tablets, like other opioids, may be diverted for non-medical use. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Oxymorphone hydrochloride extended-release tablets are intended for oral use only. Abuse of oxymorphone hydrochloride extended-release tablets pose a risk of overdose and death. This risk is increased with concurrent

abuse of oxymorphone hydrochloride extended-release tablets with alcohol and other substances. Parenteral drug abuse is commonly associated with transmission of infectious disease such as hepatitis and HIV.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

9.3 Dependence

Opioid analgesics may cause physical dependence. Physical dependence results in withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an opioid antagonist or mixed opioid agonist/antagonist agent. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity, e.g., naloxone, nalmefene, or mixed agonist/antagonist analgesics (pentazocine, butorphanol, buprenorphine, nalbuphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). The development of physical dependence and tolerance is not unusual during chronic opioid therapy.

Oxymorphone hydrochloride extended-release tablets should not be abruptly discontinued [*see Dosage and Administration (2.8)*]. If oxymorphone hydrochloride extended-release tablets are abruptly discontinued in a physically-dependent patient, an abstinence syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms [*see Use in Specific Populations (8.1, 8.2)*].

10 OVERDOSAGE

10.1 Symptoms

Acute overdosage with oxymorphone hydrochloride extended-release tablets are characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils and sometimes bradycardia and hypotension. In some cases, apnea, circulatory collapse, cardiac arrest and death may occur.

Oxymorphone hydrochloride extended-release tablets may cause miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations [*see Clinical Pharmacology (12.2)*].

10.2 Treatment

In the treatment of oxymorphone hydrochloride extended-release tablet overdosage, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

The opioid antagonist naloxone hydrochloride is a specific antidote against respiratory depression that may result from overdosage or unusual sensitivity to opioids including oxymorphone hydrochloride extended-release tablets. Nalmefene is an alternative pure opioid antagonist, which may be administered as a specific antidote to respiratory depression resulting from opioid overdose. Since the duration of action of oxymorphone hydrochloride extended-release tablets may exceed that of the antagonist, keep the patient under continued surveillance and administer repeated doses of the antagonist according to the antagonist labeling as needed to maintain adequate respiration.

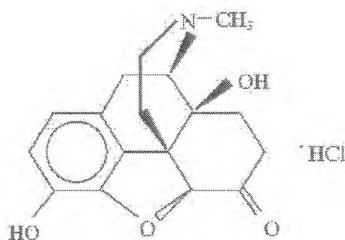
In patients receiving oxymorphone hydrochloride extended-release tablets, opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression. Administer opioid antagonists cautiously to persons who are known, or suspected to be, physically dependent on any opioid agonist including oxymorphone hydrochloride extended-release tablets. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome. In an individual physically dependent on opioids, administration of the usual dose of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. If respiratory depression is associated with muscular rigidity, administration of a neuromuscular blocking agent may be necessary to facilitate assisted or controlled ventilation. Muscular rigidity may also respond to opioid antagonist therapy.

11 DESCRIPTION

Oxymorphone hydrochloride extended-release tablets are a semi-synthetic opioid analgesic supplied in 7.5 mg and 15 mg tablet strengths for oral administration. The tablet strength describes the amount of oxymorphone hydrochloride per tablet. The tablets contain the following inactive ingredients: colloidal silicon dioxide, hypromellose, magnesium stearate, and microcrystalline cellulose. In addition, the 7.5 mg tablets contain titanium dioxide and black iron oxide. The 15 mg tablets contain titanium dioxide and yellow iron oxide.

Chemically, oxymorphone hydrochloride, USP is 4,5 α -epoxy-3, 14-dihydroxy-17-methylmorphinan-6-one hydrochloride, a white or slightly off-white, odorless powder, which is sparingly soluble in alcohol and ether, but freely soluble in water. The molecular weight of oxymorphone hydrochloride is 337.80. The pKa1 and pKa2 of oxymorphone at 37°C are 8.17 and 9.54, respectively. The octanol/aqueous partition coefficient at 37°C and pH 7.4 is 0.98.

The structural formula for oxymorphone hydrochloride is as follows:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Oxymorphone, a pure opioid agonist, is relatively selective for the mu receptor, although it can interact with other opioid receptors at higher doses.

The precise mechanism of analgesia, the principal therapeutic action of oxymorphone, is unknown. Specific central nervous system (CNS) opiate receptors and endogenous compounds with morphine-like activity have been identified throughout the brain and spinal cord and are likely to play a role in the expression and perception of analgesic effects. In addition, opioid receptors have also been identified within the peripheral nervous system (PNS). The role that these receptors play in these drugs' analgesic effects is unknown.

12.2 Pharmacodynamics

Concentration-Efficacy Relationships

The minimum effective plasma concentration of oxymorphone for analgesia varies widely among patients, especially among patients who have been previously treated with agonist opioids. As a result, individually titrate patients to achieve a balance between therapeutic and adverse effects. The minimum effective analgesic concentration of oxymorphone for any individual patient may increase over time due to an increase in pain, progression of disease, development of a new pain syndrome and/or potential development of analgesic tolerance.

Concentration-Adverse Experience Relationships

There is a general relationship between increasing opioid plasma concentration and increasing frequency of adverse experiences such as nausea, vomiting, CNS effects, and respiratory depression.

As with all opioids, the dose of oxymorphone hydrochloride extended-release tablets must be individualized [*see Dosage and Administration (2.1)*]. The effective analgesic dose for some patients will be too high to be tolerated by other patients.

Effects on the Central Nervous System (CNS)

The principal therapeutic action of oxymorphone is analgesia. In common with other opioids, oxymorphone causes respiratory depression, in part by a direct effect on the brainstem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to both increases in carbon dioxide tension and electrical stimulation. Opioids depress the cough reflex by direct effect on the cough center in the medulla.

Oxymorphone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations [*see Overdosage (10.1)*]. Other therapeutic effects of oxymorphone include anxiolysis, euphoria and feeling of relaxation.

In addition to analgesia, the widely diverse effects of oxymorphone include drowsiness, changes in mood, decreased gastrointestinal motility, nausea, vomiting, and alterations of the endocrine and autonomic nervous system [*see Clinical Pharmacology (12.1)*].

Effects on the Gastrointestinal Tract and on Other Smooth Muscle

Gastric, biliary and pancreatic secretions are decreased by oxymorphone. Oxymorphone causes a reduction in motility and is associated with an increase in tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone is increased to the point of spasm. The end result may be constipation. Oxymorphone can cause a marked increase in biliary tract pressure as a result of spasm of the sphincter of Oddi, and transient elevations in serum amylase. Oxymorphone may also cause spasm of the sphincter of the urinary bladder.

Cardiovascular System Effects

Opioids produce peripheral vasodilation which may result in orthostatic hypotension. Release of histamine can occur and may contribute to opioid-induced hypotension. Manifestations of histamine release may include orthostatic hypotension, pruritus, flushing, red eyes, and sweating. Animal studies have shown that oxymorphone has a lower propensity to cause histamine release than other opioids.

Endocrine System Effects

Opioid agonists have been shown to have a variety of effects on the secretion of hormones. Opioids inhibit the secretion of ACTH, cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon in humans and other species, rats and dogs. Thyroid stimulating hormone (TSH) has been shown to be both inhibited and stimulated by opioids.

Immune System Effects

Opioids have been shown to have a variety of effects on components of the immune system in *in vitro* and animal models. The clinical significance of these findings is unknown.

12.3 PharmacokineticsAbsorption

The absolute oral bioavailability of oxymorphone is approximately 10%.

Steady-state levels are achieved after three days of multiple dose administration. Under both single-dose and steady-state conditions, dose proportionality has been established for the 5 mg, 10 mg, 20 mg, and 40 mg doses of

oxymorphone hydrochloride extended-release tablets, for both peak plasma levels (C_{max}) and extent of absorption (AUC) (see Table 4).

Table 4: Mean (\pm SD) Oxymorphone Hydrochloride Extended-Release Pharmacokinetic Parameters

Regimen	Dosage	C_{max} (ng/mL)	AUC (ng·hr/mL)	$T_{1/2}$ (hr)
Single Dose	5 mg	0.27 \pm 0.13	4.54 \pm 2.04	11.30 \pm 10.81
	10 mg	0.65 \pm 0.29	8.94 \pm 4.16	9.83 \pm 5.68
	20 mg	1.21 \pm 0.77	17.81 \pm 7.22	9.89 \pm 3.21
	40 mg	2.59 \pm 1.65	37.90 \pm 16.20	9.35 \pm 2.94
Multiple Dose ^a	5 mg	0.70 \pm 0.55	5.60 \pm 3.87	NA
	10 mg	1.24 \pm 0.56	9.77 \pm 3.52	NA
	20 mg	2.54 \pm 1.35	19.28 \pm 8.32	NA
	40 mg	4.47 \pm 1.91	36.98 \pm 13.53	NA

NA = not applicable

^a Results after 5 days of q12h dosing.

Food Effect

Two studies examined the effect of food on the bioavailability of single doses of 20 and 40 mg of oxymorphone hydrochloride extended-release tablets in healthy volunteers. In both studies, after the administration of oxymorphone hydrochloride extended-release tablets, the C_{max} was increased by approximately 50% in fed subjects compared to fasted subjects. A similar increase in C_{max} was also observed with oxymorphone solution.

The AUC was unchanged in one study and increased by approximately 18% in the other study in fed subjects following the administration of oxymorphone hydrochloride extended-release tablets. Examination of the AUC suggests that most of the difference between fed and fasting conditions occurs in the first four hours after dose administration. After oral dosing with a single dose of 40 mg, a peak oxymorphone plasma level of 2.8 ng/ml is achieved at 1 hour in fasted subjects and a peak of 4.25 ng/ml is achieved at 2 hours in fed subjects and that beyond the 12 hour time point, there is very little difference in the curves. As a result, oxymorphone hydrochloride extended-release tablets should be dosed at least one hour prior to or two hours after eating [see *Dosage and Administration* (2.2)].

Ethanol Effect

In Vivo Oxymorphone Hydrochloride Extended-Release Tablets Formulation-Alcohol Interaction

Although *in vitro* studies have demonstrated that oxymorphone hydrochloride extended-release tablets do not release oxymorphone more rapidly in 500 mL of 0.1N HCl solutions containing ethanol (4%, 20%, and 40%), there is an *in vivo* interaction with alcohol. An *in vivo* study examined the effect of alcohol (40%, 20%, 4% and 0%) on the bioavailability of a single dose of 40 mg of oxymorphone hydrochloride extended-release tablets in healthy, fasted volunteers. The results showed that the oxymorphone mean AUC was 13% higher (not statistically significant) after co-administration of 240 mL of 40% alcohol. The AUC was essentially unaffected in subjects following the co-administration of oxymorphone hydrochloride extended-release tablets and ethanol (240 mL of 20% or 4% ethanol).

There was a highly variable effect on C_{max} with concomitant administration of alcohol and oxymorphone hydrochloride extended-release tablets. The change in C_{max} ranged from a decrease of 50% to an increase of 270% across all conditions studied. Following concomitant administration of 240 mL of 40% ethanol the C_{max} increased on average by 70% and up to 270% in individual subjects. Following the concomitant administration of 240 mL of 20% ethanol, the C_{max} increased on average by 31% and up to 260% in individual subjects. Following the concomitant administration of 240 mL of 4% ethanol, the C_{max} increased 7% on average and by as much as 110% for individual subjects. After oral dosing with a single dose of 40 mg in fasted subjects, the mean peak oxymorphone plasma level is 2.4 ng/mL and the median T_{max} is 2 hours. Following co-administration of oxymorphone hydrochloride extended-release tablets and alcohol (240 mL of 40% ethanol) in fasted subjects, the mean peak oxymorphone level is 3.9 ng/mL and the median T_{max} is 1.5 hours (range 0.75 to 6 hours).

Co-administration of oxymorphone and ethanol must be avoided.

Oxymorphone may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression because respiratory depression, hypotension, and profound sedation, coma, or death may result.

Distribution

Formal studies on the distribution of oxymorphone in various tissues have not been conducted. Oxymorphone is not extensively bound to human plasma proteins; binding is in the range of 10% to 12%.

Metabolism

Oxymorphone is highly metabolized, principally in the liver, and undergoes reduction or conjugation with glucuronic acid to form both active and inactive metabolites. The two major metabolites of oxymorphone are oxymorphone-3-glucuronide and 6-OH-oxymorphone. The mean plasma AUC for oxymorphone-3-glucuronide is approximately 90-fold higher than the parent compound. The pharmacologic activity of the glucuronide metabolite has not been evaluated. 6-OH-oxymorphone has been shown in animal studies to have analgesic bioactivity. The mean plasma 6-OH-oxymorphone AUC is approximately 70% of the oxymorphone AUC following single oral doses, but is essentially equivalent to the parent compound at steady-state.

Excretion

Because oxymorphone is extensively metabolized, <1% of the administered dose is excreted unchanged in the urine. On average, 33% to 38% of the administered dose is excreted in the urine as oxymorphone-3-glucuronide and 0.25% to 0.62% excreted as 6-OH-oxymorphone in subjects with normal hepatic and renal function. In animals given radiolabeled oxymorphone, approximately 90% of the administered radioactivity was recovered within 5 days of dosing. The majority of oxymorphone-derived radioactivity was found in the urine and feces.

Pharmacokinetics in Special Populations

Elderly

The steady-state plasma concentrations of oxymorphone, 6-OH-oxymorphone, and oxymorphone-3-glucuronide are approximately 40% higher in elderly subjects (≥ 65 years of age) than in young subjects (18 to 40 years of age). On average, age greater than 65 years was associated with a 1.4-fold increase in oxymorphone AUC and a 1.5-fold increase in C_{max} . This observation does not appear related to a difference in body weight, metabolism, or excretion of oxymorphone [see *Use in Specific Populations* (8.5)].

Gender

The effect of gender was evaluated following single- and multiple-doses of oxymorphone hydrochloride extended-release tablets in male and female adult volunteers. There was a consistent tendency for female subjects to have slightly higher AUC_{ss} and C_{max} values than male subjects; however, gender differences were not observed when AUC_{ss} and C_{max} were adjusted by body weight.

Hepatic Impairment

The liver plays an important role in the pre-systemic clearance of orally administered oxymorphone. Accordingly, the bioavailability of orally administered oxymorphone may be markedly increased in patients with moderate to severe liver disease. The disposition of oxymorphone was compared in 6 patients with mild, 5 patients with moderate, and one patient with severe hepatic impairment and 12 subjects with normal hepatic function. The bioavailability of oxymorphone was increased by 1.6-fold in patients with mild hepatic impairment and by 3.7-fold in patients with moderate hepatic impairment. In one patient with severe hepatic impairment, the bioavailability was increased by 12.2-fold. The half-life of oxymorphone was not significantly affected by hepatic impairment.

Renal Impairment

Data from a pharmacokinetic study involving 24 patients with renal dysfunction show an increase of 26%, 57%, and 65% in oxymorphone bioavailability in mild (creatinine clearance 51 to 80 mL/min; n=8), moderate (creatinine clearance 30 to 50 mL/min; n=8), and severe (creatinine clearance <30 mL/min; n=8) patients, respectively, compared to healthy controls.

Drug-Drug Interactions

In vitro studies revealed little to no biotransformation of oxymorphone to 6-OH-oxymorphone by any of the major cytochrome P450 (CYP P450) isoforms at therapeutically relevant oxymorphone plasma concentrations.

No inhibition of any of the major CYP P450 isoforms was observed when oxymorphone was incubated with human liver microsomes at concentrations of $\leq 50 \mu\text{M}$. An inhibition of CYP3A4 activity occurred at oxymorphone concentrations $\geq 150 \mu\text{M}$. Therefore, it is not expected that oxymorphone, or its metabolites will act as inhibitors of any of the major CYP P450 enzymes *in vivo*.

Increases in the activity of the CYP 2C9 and CYP 3A4 isoforms occurred when oxymorphone was incubated with human hepatocytes. However, clinical drug interaction studies with oxymorphone hydrochloride extended-release tablets showed no induction of CYP450 3A4 or 2C9 enzyme activity, indicating that no dose adjustment for CYP 3A4-or 2C9-mediated drug-drug interactions is required.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term studies have been completed to evaluate the carcinogenic potential of oxymorphone in both Sprague-Dawley rats and CD-1 mice. Oxymorphone HCl was administered to Sprague-Dawley rats (2.5, 5, and 10 mg/kg/day in males and 5, 10, and 25 mg/kg/day in females) for 2 years by oral gavage. The systemic drug exposure (AUC ng•h/mL) at the 10 mg/kg/day in male rats was 0.34-fold and at the 25 mg/kg/day dose in female rats was 1.5-fold the human exposure at a dose of 260 mg/day. No evidence of carcinogenic potential was observed in rats. Oxymorphone was administered to CD-1 mice (10, 25, 75 and 150 mg/kg/day) for 2 years by oral gavage. The systemic drug exposure (AUC ng•h/mL) at the 150 mg/kg/day dose in mice was 14.5-fold (in males) and 17.3-fold (in females) times the human exposure at a dose of 260 mg/day. No evidence of carcinogenic potential was observed in mice.

Mutagenesis

Oxymorphone hydrochloride was not mutagenic when tested in the *in vitro* bacterial reverse mutation assay (Ames test) at concentrations of ≤ 5270 mcg/plate, or in an *in vitro* mammalian cell chromosome aberration assay performed with human peripheral blood lymphocytes at concentrations ≤ 5000 mcg/ml with or without metabolic activation. Oxymorphone hydrochloride tested positive in both the rat and mouse *in vivo* micronucleus assays. An increase in micronucleated polychromatic erythrocytes occurred in mice given doses ≥ 250 mg/kg and in rats given doses of 20 and 40 mg/kg. A subsequent study demonstrated that oxymorphone hydrochloride was not aneugenic in mice following administration of up to 500 mg/kg. Additional studies indicate that the increased incidence of micronucleated polychromatic erythrocytes in rats may be secondary to increased body temperature following oxymorphone administration. Doses associated with increased micronucleated polychromatic erythrocytes also produce a marked, rapid increase in body temperature. Pretreatment of animals with sodium salicylate minimized the increase in body temperature and prevented the increase in micronucleated polychromatic erythrocytes after administration of 40 mg/kg oxymorphone.

Impairment of fertility

Oxymorphone hydrochloride did not affect reproductive function or sperm parameters in male rats at any dose tested (≤ 50 mg/kg/day). The highest dose tested is ~6-fold the human dose of 40 mg every 12 hours, based on body surface area. In female rats, an increase in the length of the estrus cycle and decrease in the mean number of viable embryos, implantation sites and corpora lutea were observed at doses of oxymorphone ≥ 10 mg/kg/day. The dose of oxymorphone associated with reproductive findings in female rats is 1.2-fold the human dose of 40 mg every 12 hours based on a body surface area. The dose of oxymorphone that produced no adverse effects on reproductive findings in female rats is 0.6-fold the human dose of 40 mg every 12 hours on a body surface area basis.

14 CLINICAL STUDIES

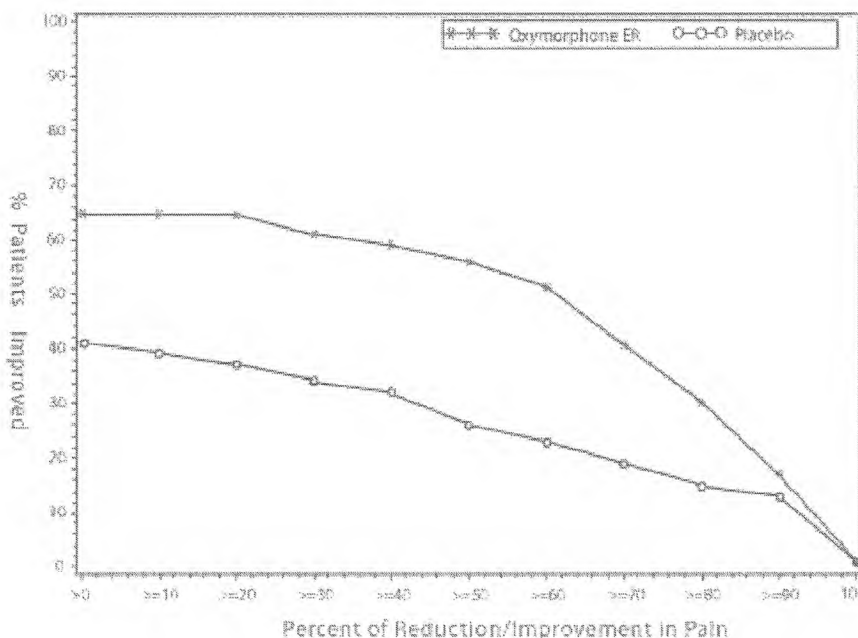
The efficacy and safety of oxymorphone hydrochloride extended-release tablets have been evaluated in double-blind, controlled clinical trials in opioid-naïve and opioid-experienced patients with moderate to severe pain including low back pain.

14.1 12-Week Study in Opioid-Naïve Patients with Low Back Pain

Patients with chronic low back pain who were suboptimally responsive to their current non-opioid therapy entered a 4-week, open-label dose titration phase. Patients initiated therapy with two days of treatment with oxymorphone hydrochloride extended-release tablets 5 mg, every 12 hours. Thereafter, patients were titrated to a stabilized dose, at increments of 5 to 10 mg every 12 hours every 3 to 7 days. Of the patients who were able to stabilize within the Open-Label Titration Period, the mean \pm SD VAS score at Screening was 69.4 \pm 11.8 mm and at Baseline (beginning of Double-Blind Period) were 18.5 \pm 11.2 mm and 19.3 \pm 11.3 mm for the oxymorphone ER and placebo groups, respectively. Sixty three percent of the patients enrolled were able to titrate to a tolerable dose and were randomized into a 12-week double-blind treatment phase with placebo or their stabilized dose of oxymorphone hydrochloride extended-release tablets. The mean \pm SD stabilized doses were 39.2 \pm 26.4 mg and 40.9 \pm 25.3 mg for the oxymorphone hydrochloride extended-release tablets and placebo groups, respectively; total daily doses ranged from 10 to 140 mg. During the first 4 days of double-blind treatment patients were allowed an unlimited number of oxymorphone hydrochloride, an immediate-release (IR) formulation of oxymorphone, 5 mg tablets, every 4 to 6 hours as supplemental analgesia; thereafter the number of oxymorphone hydrochloride was limited to two tablets per day. This served as a tapering method to minimize opioid withdrawal symptoms in placebo patients. Sixty-eight percent of patients treated with oxymorphone hydrochloride extended-release tablets completed the 12-week treatment compared to forty seven percent of patients treated with placebo. Oxymorphone hydrochloride extended-release tablets provided superior analgesia compared to placebo. The analgesic effect of oxymorphone hydrochloride extended-release was maintained throughout the double-blind treatment period in 89% of patients who completed the study. These patients reported a decrease, no change, or a \leq 10 mm increase in VAS score from Day 7 until the end of the study.

The proportion of patients with various degrees of improvement from screening to study endpoint is shown in Figure 1. The figure is cumulative, so that patients whose change from baseline is, for example, 30%, are also included at every level of improvement below 30%. Patients who did not complete the study were assigned 0% improvement.

Figure 1: Percent Reduction in Average Pain Intensity from Screening to Final Visit



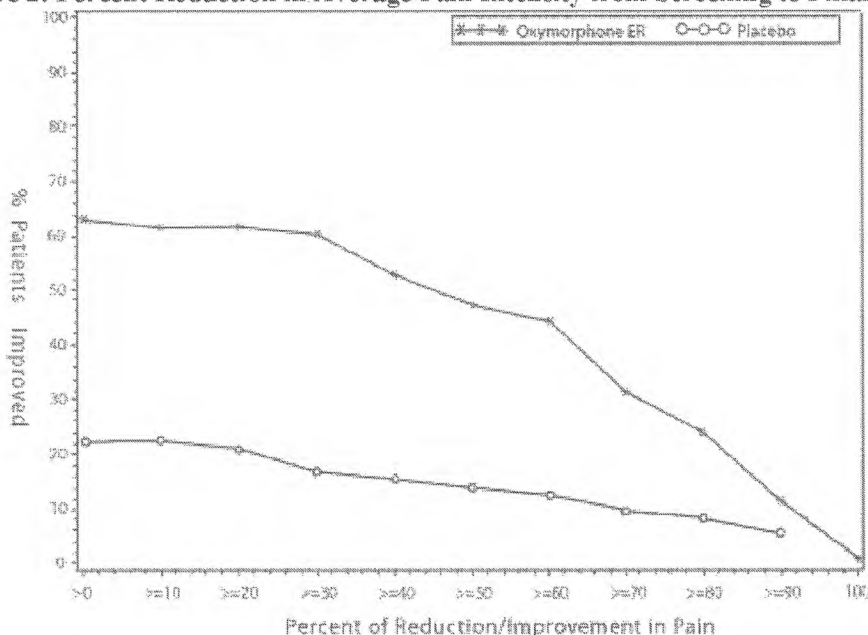
14.2 12-Week Study in Opioid-Experienced Patients with Low Back Pain

Patients currently on chronic opioid therapy entered a 4-week, open-label titration phase with oxymorphone hydrochloride extended-release tablets dosed every 12 hours at an approximated equianalgesic dose of their pre-study opioid medication. Of the patients who were able to stabilize within the Open-Label Titration Period, the mean \pm SD VAS score at Screening was 69.5 \pm 17.0 mm and at Baseline (beginning of Double-Blind Period) were

23.9±12.1 mm and 22.2±10.8 mm for the oxymorphone ER and placebo groups, respectively. Stabilized patients entered a 12-week double-blind treatment phase with placebo or their stabilized dose of oxymorphone hydrochloride extended-release tablets. The mean±SD stabilized doses were 80.9±59.3 mg and 93.3±61.3 mg for the oxymorphone hydrochloride extended-release tablets and placebo groups, respectively; total daily doses ranged from 20 to 260 mg. During the first 4 days of double-blind treatment, patients were allowed an unlimited number of oxymorphone hydrochloride 5 mg tablets, every 4 to 6 hours as supplemental analgesia; thereafter the number of oxymorphone hydrochloride tablets was limited to two tablets per day. This served as a tapering method to minimize opioid withdrawal symptoms in placebo patients. Fifty seven percent of patients were titrated to a stabilized dose within approximately 4 weeks of oxymorphone hydrochloride extended-release tablet dose titration. Seventy percent of patients treated with oxymorphone hydrochloride extended-release tablets and 26% of patients treated with placebo completed the 12-week treatment. Oxymorphone hydrochloride extended-release tablets provided superior analgesia compared to placebo. The analgesic effect of oxymorphone hydrochloride extended-release was maintained throughout the double-blind treatment period in 80 % of patients who completed the study. These patients reported a decrease, no change, or a ≤10 mm increase in VAS score from Day 7 until the end of the study.

The proportion of patients with various degrees of improvement from screening to study endpoint is shown in Figure 2. The figure is cumulative, so that patients whose change from baseline is, for example, 30%, are also included at every level of improvement below 30%. Patients who did not complete the study were assigned 0% improvement.


Figure 2: Percent Reduction in Average Pain Intensity from Screening to Final Visit



16 HOW SUPPLIED/STORAGE AND HANDLING

Oxymorphone Hydrochloride Extended-Release Tablets are supplied as follows:


7.5 mg

Gray, round tablets, debossed with “” on one side and “261” on the other side.

Bottles of 100 with a child-resistant closure.....NDC 0228-3261-11

Bottles of 500 without a child-resistant closure.....NDC 0228-3261-50

15 mg

White to off-white, round tablets, debossed with “” on one side and “262” on the other side.

Bottles of 100 with a child-resistant closure.....NDC 0228-3262-11
 Bottles of 500 without a child-resistant closure.....NDC 0228-3262-50

Oxymorphone hydrochloride extended-release tablets contain oxymorphone, which is a controlled substance. Oxymorphone is controlled under Schedule II of the Controlled Substances Act. Oxymorphone, like all opioids, is liable to diversion and misuse and should be handled accordingly. Patients and their families should be instructed to flush any oxymorphone hydrochloride extended-release tablets that are no longer needed.

Oxymorphone hydrochloride extended-release tablets may be targeted for theft and diversion. Healthcare professionals should contact their State Medical Board, State Board of Pharmacy or State Control Board for information on how to detect or prevent diversion of this product.

Healthcare professionals should advise patients to store oxymorphone hydrochloride extended-release tablets in a secure place, preferably locked and out of the reach of children and other non-caregivers.

Store at 25°C (77 F); excursions permitted to 15°-30 C (59°-86° F). [See USP Controlled Room Temperature].

Dispense in tight container as defined in the USP, with a child-resistant closure (as required).

Advise patients to dispose of any unused tablets from a prescription by flushing them down the toilet as soon as they are no longer needed [see *Patient Counseling Information* (17)].

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling

- Advise patients that oxymorphone hydrochloride extended-release tablets contain oxymorphone, a morphine-like pain reliever, and should be taken only as directed.
- Advise patients that oxymorphone hydrochloride extended-release tablets are designed to work properly only if swallowed whole. The extended-release tablets may release all their contents at once if broken, chewed or crushed, resulting in a risk of fatal overdose of oxymorphone.
- Patients must not consume alcoholic beverages, or prescription or non-prescription medications containing alcohol, while on oxymorphone hydrochloride extended-release tablets therapy. The co-ingestion of alcohol with oxymorphone hydrochloride extended-release tablets may result in increased plasma levels and a potentially fatal overdose of oxymorphone.
- Appropriate pain management requires changes in the dose to maintain best pain control. Advise patients of the need to contact their physician if pain control is inadequate, but not to change the dose of oxymorphone hydrochloride extended-release tablets without consulting their physician.
- Advise patients to report episodes of breakthrough pain and adverse experiences occurring during therapy to their doctor. Individualization of dosage is essential to make optimal use of this medication.
- Caution patients that oxymorphone hydrochloride extended-release tablets may cause drowsiness, dizziness, or lightheadedness, and may impair mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car, operating machinery, etc.
- Instruct patients not to combine oxymorphone hydrochloride extended-release tablets with alcohol or other central nervous system depressants (sleep aids, tranquilizers) except by the orders of the prescribing physician, because additive effects may occur, resulting in serious injury or death.

- Advise patients taking oxymorphone hydrochloride extended-release tablets of the potential for severe constipation. Appropriate laxatives and/or stool softeners and other therapeutic approaches may be considered for use with the initiation of oxymorphone hydrochloride extended-release tablet therapy.
- Advise patients not to adjust the dose of oxymorphone hydrochloride extended-release tablets without consulting the prescribing professional.
- Advise patients that oxymorphone hydrochloride extended-release tablets are a potential drug of abuse. They should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed.
- Advise women of childbearing potential who become, or are planning to become pregnant to consult their physician regarding the effects of opioid analgesics and other drug use during pregnancy on themselves and their unborn child.
- If patients have been receiving treatment with oxymorphone hydrochloride extended-release tablets for more than a few days to weeks and cessation of therapy is indicated, counsel them on the importance of safely tapering the dose and that abruptly discontinuing the medication could precipitate withdrawal symptoms. Provide patients with a dose schedule to accomplish a gradual discontinuation of the medication.
- As with any potent opioid, misuse of oxymorphone hydrochloride extended-release tablets may result in serious adverse events. Instruct patients to keep oxymorphone hydrochloride extended-release tablets in a secure place out of the reach of children and pets. Accidental consumption especially in children can result in overdose or death. When oxymorphone hydrochloride extended-release tablets are no longer needed, instruct patients to destroy unused tablets by flushing them down the toilet.

FDA – Approved Patient Labeling

OXYMORPHONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS CII

7.5 mg and 15 mg

IMPORTANT: Keep oxymorphone hydrochloride extended-release tablets in a safe place away from children. Accidental use by a child is a medical emergency and can result in death. If a child accidentally takes oxymorphone hydrochloride extended-release tablets, get emergency help right away.

Read the Patient Information that comes with oxymorphone hydrochloride extended-release tablets before you start taking it and each time you get a new prescription. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment. Share the important information in this leaflet with members of your household.

What Is the Most Important Information I Should Know About Oxymorphone Hydrochloride Extended-Release Tablets?

- **Oxymorphone hydrochloride extended-release tablets can cause trouble breathing (hypoventilation),** which can lead to death, if used differently than the way you were told to use it by your healthcare provider (see “What are the possible side effects of oxymorphone hydrochloride extended-release tablets?”).
- **Swallow oxymorphone hydrochloride extended-release tablets whole.** Do not break, crush, dissolve, or chew oxymorphone hydrochloride extended-release tablets before swallowing. **If a tablet is broken, crushed, dissolved, or chewed, the full 12 hour dose can be taken into your body all at once. This is very dangerous. You could die from an overdose of the medicine.** Use oxymorphone hydrochloride extended-release tablets exactly the way your healthcare provider prescribes. If you cannot swallow tablets whole, tell your healthcare provider. You may need a different medicine.

- **Do not consume alcoholic beverages, or prescription or non-prescription medications containing alcohol, while taking oxymorphone hydrochloride extended-release tablets.**

What are Oxymorphone Hydrochloride Extended-Release Tablets?

- Oxymorphone hydrochloride extended-release tablets are a prescription medicine that contains the opioid (narcotic pain medicine) oxymorphone. Oxymorphone hydrochloride extended-release tablets are used to treat adults with constant pain (around the clock) that is moderate to severe and is expected to last for an extended period of time. **Oxymorphone hydrochloride extended-release tablets are not for occasional (—as needed”) use.**
- **Oxymorphone hydrochloride extended-release tablets can cause physical dependence.** Do not stop taking oxymorphone hydrochloride extended-release tablets all of a sudden if you have been taking it for more than a few days. You could become sick with uncomfortable withdrawal symptoms because your body has become use to the medicine. Talk to your healthcare provider about slowly stopping oxymorphone hydrochloride extended-release tablets to avoid getting sick with withdrawal symptoms. Physical dependence is not the same as drug addiction. Your healthcare provider can tell you more about the differences between physical dependence and drug addiction.
- **Oxymorphone hydrochloride extended-release tablets are a controlled substance (CII) because they contain a narcotic painkiller** that can be a target for people who abuse prescription medicines or street drugs. Keep your tablets in a safe place to protect them from being stolen. Never give your tablets to anyone else, even if they have the same symptoms you have. Selling or giving away this medicine may harm others, even causing death, and is against the law.

Who Should Not Take Oxymorphone Hydrochloride Extended-Release Tablets?

Do not take oxymorphone hydrochloride extended-release tablets if:

- You had surgery within the past day (24 hours) and you were not taking oxymorphone hydrochloride extended-release tablets before your surgery.
- Your pain is mild or will go away in a few days.
- Your pain can be controlled by the occasional use of other pain medicines.
- You are having an asthma attack or have severe asthma, trouble breathing, or lung problems.
- You have liver problems.
- You are allergic to oxymorphone hydrochloride extended-release tablets or anything in them. See the end of this leaflet for a complete list of ingredients in oxymorphone hydrochloride extended-release tablets.
- You have had severe allergic reactions to other narcotic pain medicines (such as morphine or codeine medicines). A severe allergic reaction includes a severe rash, hives, breathing problems, or dizziness.

Oxymorphone hydrochloride extended-release tablets are not for children under 18 years of age.

What Should I Tell My Healthcare Provider Before Starting Oxymorphone Hydrochloride Extended-Release Tablets?

Tell your healthcare provider about all of your medical problems, especially if you:

- have trouble breathing or lung problems
- have a head injury or brain problems
- have liver or kidney problems
- have adrenal gland problems, such as Addison’s disease
- have convulsions or seizures
- have thyroid problems
- have problems urinating or prostate problems
- have pancreas problems
- have a drinking problem or alcoholism
- have severe mental problems or hallucinations (see or hear things that are not really there)
- have past or present drug abuse or drug addiction problems

- **are pregnant or plan to become pregnant.** Oxymorphone hydrochloride extended-release tablets may harm your unborn baby.
- **are breastfeeding.** Oxymorphone hydrochloride extended-release tablets may pass through your milk and may harm your baby. You should not breastfeed while taking oxymorphone hydrochloride extended-release tablets.

Tell your healthcare provider about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines may cause serious problems when taken with oxymorphone hydrochloride extended-release tablets, especially if they cause sleepiness (like sleeping pills, anxiety medicines, antihistamines, or tranquilizers).

Do not take any new medicines while using oxymorphone hydrochloride extended-release tablets until you have talked to your healthcare provider or pharmacist and they have told you it is safe.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist.

How Should I Take Oxymorphone Hydrochloride Extended-Release Tablets?

- **Follow your healthcare provider's directions exactly.** Your healthcare provider may change your dose based on your reactions to the medicine. Do not change your dose unless your healthcare provider tells you to change it. Do not take oxymorphone hydrochloride extended-release tablets more often than prescribed.
- **Swallow oxymorphone hydrochloride extended-release tablets whole. Do not break, crush, dissolve, or chew oxymorphone hydrochloride extended-release tablets before swallowing. If a tablet is broken, crushed, dissolved, or chewed, the full 12 hour dose can be taken into your body all at once. This is very dangerous. You could die from an overdose of the medicine.** If you cannot swallow tablets whole, tell your healthcare provider. You may need a different medicine.
- Take oxymorphone hydrochloride extended-release tablets every 12 hours or as instructed by your healthcare provider. Oxymorphone hydrochloride extended-release tablets should be taken on an empty stomach, at least one hour before or two hours after meals. Talk to your healthcare provider if you feel sick taking oxymorphone hydrochloride extended-release tablets on an empty stomach.
- **If you miss a dose,** take it as soon as possible. If it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. **Do not take 2 doses at once unless your healthcare provider tells you to.** If you are not sure about your dosing call your healthcare provider.
- **If you take too much oxymorphone hydrochloride extended-release tablets or overdose,** call your local emergency number or poison control center right away.
- **Talk to your healthcare provider often about your pain.** Your healthcare provider can decide if you still need oxymorphone hydrochloride extended-release tablets.
- **If you have side effects that bother you or if you continue to have pain, call your healthcare provider.**
- **Stopping oxymorphone hydrochloride extended-release tablets.** If your healthcare provider decides you no longer need oxymorphone hydrochloride extended-release tablets, ask how to slowly reduce the dose of your medicine so you don't get uncomfortable (withdrawal) symptoms such as nausea, sweating, and pain. You should not stop taking oxymorphone hydrochloride extended-release tablets all at once if you have been taking it for more than a few days without talking to your healthcare provider. Oxymorphone hydrochloride extended-release tablets can cause physical dependence. You can get sick with withdrawal symptoms if you stop oxymorphone hydrochloride extended-release tablets all at once, because your body has become use to it.

After you stop taking oxymorphone hydrochloride extended-release tablets, flush the unused tablets down the toilet. Safely dispose of oxymorphone hydrochloride extended-release tablets out of the reach of children and pets.

What Should I Avoid While Taking Oxymorphone Hydrochloride Extended-Release Tablets?

- **Do not drive, operate heavy machinery, or participate in any other possibly dangerous activities until you know how you react to this medicine.** Oxymorphone hydrochloride extended-release tablets can make you sleepy. Ask your healthcare provider to tell you when it is okay to do these activities.
- **Do not drink alcohol while using oxymorphone hydrochloride extended-release tablets.** It may increase the chance of having dangerous side effects including overdose and death.

What are the Possible Side Effects of Oxymorphone Hydrochloride Extended-Release Tablets?

Oxymorphone hydrochloride extended-release tablets can cause trouble breathing.

Call your healthcare provider or get medical help right away if:

- your breathing slows down
- you have shallow breathing (little chest movement with breathing)
- you feel faint, dizzy, confused, or have any other unusual symptoms

These can be signs that you have taken too many oxymorphone hydrochloride extended-release tablets (overdose) or the dose is too high for you, which can be dangerous and lead to death if not treated.

Oxymorphone hydrochloride extended-release can cause your blood pressure to drop. This can make you feel dizzy if you get up too fast from sitting or lying down. Low blood pressure is also more likely to happen if you are taking other medicines that can also lower your blood pressure.

Oxymorphone hydrochloride extended-release can cause physical dependence. Your body will get used to oxymorphone hydrochloride extended-release if you take it more than a few days. You can get sick with withdrawal symptoms if you stop taking oxymorphone hydrochloride extended-release tablets all at once. You can avoid getting sick with withdrawal symptoms by stopping oxymorphone hydrochloride extended-release tablets slowly. Your healthcare provider will tell you how to do this.

There is a chance of abuse or addiction with oxymorphone hydrochloride extended-release tablets. Abuse or addiction is different than a physical dependence. If you have abused prescription medicines, street drugs or alcohol in the past, you may have a higher chance of developing abuse or addiction again while using oxymorphone hydrochloride extended-release tablets. If you have more concerns, talk to your healthcare provider for more information about abuse and addiction.

The most common side effects of oxymorphone hydrochloride extended-release tablets are nausea, constipation, dizziness, vomiting, itching, sleepiness, headache, increased sweating, and sedation. Some of these side effects may decrease with continued use. Talk to your healthcare provider if you continue to have these side effects.

These are not all the possible side effects of oxymorphone hydrochloride extended-release tablets. For a complete list, ask your healthcare provider or pharmacist.

Constipation (decrease in the usual number of hard bowel movements) is a common side effect of opioid medicines, including oxymorphone hydrochloride extended-release tablets. Talk to your healthcare provider or pharmacist about the use of laxatives (medicines to treat constipation) and stool softeners to prevent or treat constipation while taking oxymorphone hydrochloride extended-release tablets.

How should I store Oxymorphone Hydrochloride Extended-Release Tablets?

- Store oxymorphone hydrochloride extended-release tablets at room temperature between 59° to 86°F (15° to 30°C).
- Keep oxymorphone hydrochloride extended-release tablets in a childproof container and store in a safe place to protect it from being stolen.
- **Keep oxymorphone hydrochloride extended-release tablets out of the reach of children. Accidental overdose in children is an emergency and can result in death.**

General Information about Oxymorphone Hydrochloride Extended-Release Tablets

- Do not use oxymorphone hydrochloride extended-release tablets for conditions for which they were not prescribed.
- Do not give oxymorphone hydrochloride extended-release tablets to other people, even if they have the same symptoms you have. It may harm them, even causing death, and it is against the law.

This leaflet summarizes the most important information about oxymorphone hydrochloride extended-release tablets. If you would like more information, talk with your healthcare provider. Also, you can ask your pharmacist or healthcare provider for information about oxymorphone hydrochloride extended-release tablets that is written for healthcare professionals.

What are the ingredients in Oxymorphone Hydrochloride Extended-Release Tablets?

Active Ingredient: oxymorphone hydrochloride

Inactive Ingredients: colloidal silicon dioxide, hypromellose, magnesium stearate, and microcrystalline cellulose. In addition, the 7.5 mg tablets contain titanium dioxide and black iron oxide. The 15 mg tablets contain titanium dioxide and yellow iron oxide.

Rx Only

Manufactured by
Actavis Elizabeth LLC
200 Elmora Avenue
Elizabeth, NJ 07207 USA

40-9144

Revised - October 2010



Introduction of Oxymorphone Hydrochloride Extended-Release Tablets, CII





The Latest News from Actavis

Actavis launches generic Oxymorphone Hydrochloride Extended-Release Tablets, CII 7.5mg and 15mg (AB-rated to Opana ER®*) in July

...and we'd like your help to increase awareness regarding the availability of this new product!



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Oxymorphone Overview

- Oxymorphone Hydrochloride Extended-Release Tablets, CII is available from Actavis in 7.5mg and 15mg, bottles of 100's.
- AB-rated to Opana ER® by Endo Labs.
- Opana ER was originally available in 7 strengths: 5mg, 7.5mg, 10mg, 15mg, 20mg, 30mg and 40mg.
- Endo discontinued the 7.5mg and 15mg strengths in March, 2011. *Endo did not withdraw these strengths due to safety reasons.*
- We believe that Actavis is the first, and perhaps only, generic available in the 7.5mg and 15mg strengths at initial launch.
- Product launched on July 15th, shipped to all major wholesalers.



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Prescription Data

Average Monthly TRx				
Strength	Jan-Mar 2011 Average TRx	Apr 2011 TRx	May 2011 TRx	Jun 2011 TRx
15mg	5760	4188	2515	1595
7.5mg	1340	793	511	320
Total TRx	7100	4981	3026	1915

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Marketing Support

- A two wave **direct-mail campaign** to the top 10,000 prescribing doctors. The first wave is planned to coincide with our launch to bring awareness to prescribing doctors. A follow-up mailing is planned early September.
- **Journal advertising** to cover both prescribers and pharmacists:
 - Practical Pain Management - focused on pain specialists. Circulation: 45,000. Insertion in August 2011 issue and October 2011 back cover.
 - Pharmacy Times - focused on Pharmacists/Pharmacy buyers. Circulation: 163,500. Insertion in August 2011 issue.
- **Email campaign** reaching a pharmacy audience of 87,000 addresses.
- Using **Kadian detail sales team** to deliver generic availability message to pain doctors.



Sell Sheet - front & back

Generic is now available.



Oxycodone Hydrochloride Extended-Release Tablets, CII

Actavis is proud to launch Oxycodone Hydrochloride Extended-Release Tablets, CII 7.5 mg and 15 mg strengths, immediately available. It is AB rated to Opana® ER Oxycodone Hydrochloride Extended-Release Tablets and is indicated for the relief of moderate to severe pain in patients requiring continuous around-the-clock opioid treatment for an extended period of time. At Actavis, we are working to meet the demand for high quality lower-cost alternatives to brand name pharmaceuticals.

Please see the following *Black Box Warning* and attached for full prescribing information.

IMPORTANT SAFETY INFORMATION
Oxycodone Hydrochloride extended-release tablets contain oxycodone, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid agonists. Oxycodone can be abused to a manifest extent to achieve opioid agonist, legal or illicit. This should be considered when prescribing or dispensing oxycodone hydrochloride extended-release tablets. In addition, when the physician or pharmacist is concerned about the risk of misuse, abuse, or diversion, Oxycodone Hydrochloride extended-release tablets are an opioid agonist indicated for the relief of moderate to severe pain in patients requiring continuous around-the-clock opioid treatment for an extended period of time. Oxycodone Hydrochloride extended-release tablets are NOT intended for use as an as-needed analgesic. Oxycodone Hydrochloride extended-release tablets are not to be crushed, chewed, dissolved, or crushed and dissolved to rapidly release and absorption of a potentially fatal dose of oxycodone. Patients must avoid consuming alcohol, benzodiazepines, tranquilizers or other depressants as well as alcohol. Consumption of alcohol with oxycodone Hydrochloride extended-release tablets may result in a potentially fatal overdose of oxycodone.

Loading this way...with quality generics.

Results drive our Actavis customer service at 800.426.2842, or visit www.actavis.com.

Actavis logo

Now available from Actavis



Oxycodone Hydrochloride Extended-Release Tablets, CII

- Generic is available in 7.5mg and 15mg strengths
- AB Rated, to Opana ER®
- 100-count bottles
- Another addition to our expanding product portfolio

Product	Strength	Size	NDC#
Oxycodone Hydrochloride Extended-Release Tablets, CII	7.5 mg	100	0220-2261-11
Oxycodone Hydrochloride Extended-Release Tablets, CII	15 mg	100	0220-2262-11

To learn more, contact your Actavis representative or wholesaler, or call customer service at 800.426.2842.

Please see attached for full prescribing information.

Actavis logo



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Thank you!

